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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,360	11/03/2005	Maximilian Grassberger	PD/4-32806A	1352

1095 7590 01/24/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
HOUGHTLING, RICHARD A	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
01/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,360	GRASSBERGER ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *23 November 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5 are pending in the application received 03 November 2005, and herein are examined on their merits.

Foreign Priority

2. Applicants' claim to foreign priority to GB 0307869.8 under 35 U.S.C. 119(a)-(d) is acknowledged; a certified copy was filed 23 September 2005.

Information Disclosure Statements

3. Receipt of an information disclosure statement filed by applicants on 23 September 2005 is acknowledged; examiner entered disclosures into the record and references were considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner notes that Applicants' claim 3 is drawn to a method comprising co-administering a synergistically effective amount of a composition according to claim 1, which is a pharmaceutical composition comprising 33-epichloro-33-desoxyascomycin in combination or association with a local anesthetic, together with at least one pharmaceutically acceptable diluent or carrier.

Applicants' disclosure does not provide a working example demonstrating a method for treatment of a dermatological disease comprising administering a pharmaceutical composition of 33-epichloro-33-desoxyascomycin in combination or association with a local anesthetic. Furthermore, the disclosure does not provide any evidentiary support that synergistic effects are obtained for treatment of dermatological diseases. Instead, Applicants' disclose an equation to calculate synergism using an index of synergy, whereby, a calculated value (x), in a ratio of: $x < 1$, is synergistic; $x = 1$, is additive; and $x > 1$, is antagonistic. In lieu of any evidence to the contrary, the Examiner cannot ascertain whether Applicants' claim to a method for treatment of dermatological diseases by co-administering synergistically effective amounts of 33-epichloro-33-desoxyascomycin and a local anesthetic exist.

5. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of contact dermatitis, does not reasonably provide enablement for prevention, prophylaxis as well as curative treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

According to Stedman's Concise Medical Dictionary (1987), the term "prophylactic" is defined as 1) preventive, preventing disease or 2) an agent that acts as a preventive against disease (p. 613, col. 2, lines 35-41); while, "preventive" is defined as 1) prophylactic 2) anything that *arrests the threatened onset of disease* (p. 607, col.2, lines 53-56). Using the common medical definitions of prophylaxis as preventive, applicants' specification fails to provide enough detailed teachings for an artisan to use the invention commensurate within the scope of the claims.

The instant claims are drawn to a method for the "treatment" of dermatological diseases, wherein Applicants' definition of "treatment" defined by Applicants' (see p. 5) to include prevention, prophylaxis and curative treatment (see p. 5), and therefore the scope of claim 3 encompasses prevention of dermatological diseases and cures. of a common cold. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider

when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant invention pertains to a method of preventing or curing dermatological diseases in a subject suffering from or "at risk for such condition," comprising co-administering an additive/synergistically effective amount of a composition comprising 33-epichloro-33-desoxyascomycin in combination or association with a local anesthetic, together with at least one pharmaceutically acceptable carrier or diluent.

Breadth of the claims: The instant claims embrace preventing, curing or treating dermatological diseases.

State of prior art: The state of the art for a method for treatment of symptoms of various dermatological diseases is reasonably established in the prior art, however, a

method for prevention of dermatological diseases (i.e. eczema or psoriasis) which must be completely, totally, absolutely, or permanently eradicated so that it has been prevented is highly unlikely and therefore not developed in the prior art.

Relative skill of those in the art: The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art: The skilled artisan would view that the method for treating symptoms of dermatological diseases relatively predictable; however, in order to prevent or cure the development of dermatological is highly unpredictable. As such, applicant must demonstrate that the invention is able to arrest each and every known and unknown cause of dermatological diseases, as well as demonstrate that it works in these patient populations, so as to completely prevent or to completely cure a dermatological disease.

Amount of guidance provided by the inventor and existence of working examples: In the instant case, working examples are provided in the specification, as filed, for making the pharmaceutical composition as a cream or a gel, but does not provide an example demonstrating how to use applicants' invention for treatment of any dermatological disease, nor examples which teach a method for the prevention or the cure of a dermatological disease. Note that lack of a working example, is a critical

factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the *Wands* factors, e.g., the lack of direction or guidance provided, an absence of working examples, undeveloped and unpredictable prior art as discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in *undue experimentation* to determine if applicant's invention actually function as claimed with no assurance of success. Therefore, the claims are not considered enabled for the prevention or cure of dermatological diseases.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ormerod et al. (WO 99/24036, as found in PTO-1449 dated 23 September 2005) and further in view of Egekvist et al. (2000, see PTO-892) and Stymne et al. (2001, see PTO-892).

Applicants' invention is drawn to a pharmaceutical composition (claims 1-2), a method for treatment of dermatological diseases (claim 3), a process of making the pharmaceutical composition (claim 4) and a kit of parts comprising separate dosage forms together with instructions for use (claim 5). The pharmaceutical composition

comprises a macrolide in combination or association with a local anesthetic, together with at least one pharmaceutically acceptable diluent or carrier.

Ormerod et al. teach topical formulations, manufacture of a topical formulation and method for treatment of a dermatological condition comprising an immunosuppressive macrolide and a permeation modulator, which when applied to the skin produces a minimal systemic effect (see abstract). Specifically, the immunosuppressive macrolides taught include: sirolimus, FK-506 or SDZ ASM-981, which is also known as 33-epi-chloro-33-desoxyascomycin (see p. 5, lines 3-4). In Example 3, topical sirolimus formulation applied to the skin of patients with chronic plaque psoriasis result in clinical improvement (see results found in Table 3, p. 14). It is well-established in the prior art that systemic administration of macrolide immunosuppressants are associated with undesirable side effects when taken systemically for treating dermatological diseases, such as, psoriasis or atopic dermatitis (p. 3, lines 13-17). Thus, Ormerod et al. overcome the problem associated with systemic administration by formulation of topical macrolide immunosuppressants which reach the site of action via the incorporation of the permeation modulator.

Ormerod et al. does not teach the local anesthetics or the combination of macrolide immunosuppressive agents and local anesthetics.

Egekvist et al. (2000) teach the analgesic effects of EMLA cream (oil-in-water emulsion composed of prilocaine 2.5%, lidocaine 2.5%, and an emulsifier) applied to the skin. The analgesic effects of EMLA cream are due to the local anesthetic effects of prilocaine and lidocaine at cutaneous and subcutaneous nociceptors and free nerve endings (see p. 340, 1st ¶). In addition to the local anesthetic effects, prilocaine and lidocaine treatment also constricts superficial capillary vessels and subcutaneous veins (p. 341, Table 1 and Results section 1st ¶).

Egekvist et al. does not teach use of local anesthetics for treatment of dermatological disease or use of a macrolide immunosuppressant.

Stymne et al. (2001) teach clinical benefit of application of the local anesthetics—lidocaine and prilocaine (EMLA) to patients suffering from acute-treatment-related pain following debridement of leg ulcerations which lasts at least 4 hr (p. 534, lines 13-16). Furthermore, these studies show limited systemic levels of the local anesthetics even following 24 hour administration (see p. 532, Figure 2, and p. 534, col. 1, lines 36-41). Together, these data indicate that the long-term analgesic effects of the EMLA therapy are likely mediated by restricted systemic absorption (see p. 534, lines 13-18).

Stymne et al. does not teach the combination of local anesthetics and a macrolide.

Ormerod et al. taught that it is undesirable to use systemic dosing of macrolide immunosuppressants such as, sirolimus or SDZ-ASM-981, for dermatological diseases. One of ordinary skill in the art seeking to improve the topical formulation taught by Ormerod et al. would have been motivated to include local anesthetics by the teachings of Egekvist et al. and Stymne et al., which demonstrated the ability of the local anesthetic to both reduce cutaneous circulation and provide analgesic effects for the pain which often accompany dermatological diseases such as psoriasis, atopic dermatitis, rosacea or post-peel, thus resulting in the pharmaceutical composition of instant claims 1 or 2.

Furthermore, one of ordinary skill in the art would have found it obvious to use the pharmaceutical composition described above for treatment of dermatological diseases as is suggested by Ormerod et al. and to further determine synergistic effective amounts. The combination of the local anesthetic and the topical macrolide immunosuppressant, SDZ-ASM 981 (33-epi-chloro-33-desoxyascomycin) would increase in the local concentration of the macrolide; and therefore, it would have been obvious to one of ordinary skill in the art to make adjustments to the particular conventional working conditions (e.g., determining result effective amounts of the ingredients beneficially taught by the cited references), as well as treating a particular type of dermatological disease, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan and no more than an effort to optimize results.

Applicants claim 4 drawn to a process of preparation of a composition according to mixing a macrolide and a local anesthetic with at least one pharmaceutically acceptable carrier is obvious to one of ordinary skill in the art as the end product may be made by many different processes which result in the same product. For example, the local anesthetic cream described in Stymne et al. could be modified by mixing in the macrolide antibiotic resulting in a pharmaceutical composition of the instant claim.

7. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ormerod et al. (WO 99/24036, as found in PTO-1449 dated 23 September 2005) and further in view of Egekvist et al. (2000, see PTO-892) and Stymne et al. (2001, see PTO-892) as applied to claims 1-4 above, and further in view of *Remington's: The Science and Practice of Pharmacy*, Nineteenth Edition, Vol I, 1985, p. 806.

Ormerod et al., Egekvist et al., and Stymne et al. do not teach a kit comprising 33-epi-chloro-33-desoxyascomycin and a local anesthetic with printed instructions.

Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol I, 1985, p. 806 teaches that the inclusion of a package insert including "indications and use" of the pharmaceutical composition is mandated by 21 CFR 201.57.

At the time of Applicants' invention, it would have been obvious to one of ordinary skill in the art to include a label and packaging in the composition of Ormerod et al., Ekgvist et al., and Stymne et al. One of ordinary skill in the art would have been motivated to include the packaging and the insert, because it is mandated by law as taught in Remington's.

It is well-settled law that combining printed instructions and an old product into a kit will not render the claimed invention nonobvious even if the instructions detail a new use for the product. See In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). Further, the inclusion of a package insert or label showing the "the name of drug, dosage, dosage form, route of administration, indication and direction of use" of a pharmaceutical composition is mandated by 21 CFR 201.57 and is therefore obvious to one of ordinary skill in the art.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling whose telephone number is (571) 272-9334. The examiner may normally be reached Mon-Thurs 8:30 am - 5:00 pm and alternate Fridays 8:30 am - 12:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan may be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard A. Houghtling, Ph.D.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER